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Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: a case report

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Abstract: Background: Relapses after therapy with direct-acting antiviral agents (DAA) in chronic hepatitis C virus (HCV) infections are rare due to high efficacy of interferon-free therapy regimens. The presence of resistance-associated substitutions (RAS) in proteins targeted by therapy can lead to lower rates of sustained virological response (SVR) in patients receiving DAA-therapy, and little evidence exists as to how to treat these patients. Case summary: We present a case of a multi-drug-resistant HCV-genotype-3a-infection in a 50-year-old female without confirmed cirrhosis but with advanced fibrosis (liver stiffness 11.6 kPa) and low viral load. Resistance testing revealed a Y93H mutation in the NS5A gene. Therapies using sofosbuvir and daclatasvir (1st), sofosbuvir, velpatasvir and ribavirin (2nd), and subsequently with sofosbuvir, velpatasvir, and voxilaprevir (3st) did not achieve SVR. Compliance was good with rapid negativity of HCV RNA at 4 weeks of treatment on all 3 occasions. No virological breakthrough was recorded with all regimens. As a rescue attempt, the patient received 24 weeks of sofosbuvir, glecaprevir/pibrentasvir, and weight-based ribavirin at 1000 mg. With this approach, she achieved SVR but developed hepatocellular carcinoma. Conclusion: The combination of sofosbuvir, glecaprevir/pibrentasvir and ribavirin could be a rescue therapy after previous relapses on DAA-therapy, especially in patients with relapse after therapy with sofosbuvir, velpatasvir, and voxilaprevir.

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**Erfolgreiche Viertlinien-Therapie einer Patientin mit chronischer Hepatitis C
Virusinfektion mit Sofosbuvir, Glecaprevir/Pibrentasvir und Ribavirin:
Ein Fallbericht**

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Schlüsselwörter: Chronische Hepatitis C Virusinfektion, direkt-antiviral wirkende Substanzen, Resistenz-assoziierte Mutationen, Voxilaprevir Therapieversagen, Fallbericht

Details und Kommentare: Es wird bestätigt, dass das vorliegende Manuskript weder veröffentlicht noch anderweitig zur Veröffentlichung eingereicht ist. Die Erstellung erfolgte in Übereinstimmung mit der Erklärung von Helsinki.

Abstract (Deutsch)

Hintergrund: Rückfälle nach einer Therapie mit direkt-antiviral wirkenden Substanzen (DAA) bei Patienten mit chronischer Virushepatitis C (HCV) sind aufgrund der hohen Wirksamkeit dieser Therapeutika selten. Das Auftreten von Resistenz-assoziierten Substitutionen (RAS) in Proteinen auf welche die Therapie abzielt, kann eine anhaltende Viruselimination (SVR) verhindern und es existiert wenig Evidenz wie diese Patienten anschließend behandelt werden sollten.

Fallbeschreibung: Wir berichten von einer 50-jährigen Patientin mit einer therapieresistenten HCV Genotyp 3a Infektion ohne bestätigte Leberzirrhose, aber mit fortgeschrittener Fibrose (Lebersteifigkeit 11,6kPa) und niedriger Viruslast. Resistenztestungen zeigten eine Y93H-Mutation im NS5A-Gen des Virus. Mehrere Therapieversuche mit Sofosbuvir und Daclatasvir (1.), Sofosbuvir, Velpatasvir und Ribavirin (2.) und mit Sofosbuvir, Velpatasvir und Voxilaprevir (3.) konnten kein SVR erreichen. Es ergaben sich keine Hinweise auf eine eingeschränkte Compliance, da es jeweils nach vier Wochen zu einer schnellen und über den Therapiezeitraum persistierenden Negativierung der Viruslast kam. Als letzte Alternative erhielt die Patientin eine 24-wöchige Therapie mit Sofosbuvir, Glecaprevir/Pibrentasvir und gewichtsadaptiert 1000mg Ribavirin. Damit erreichte sie ein SVR, entwickelte aber ein hepatozelluläres Karzinom.

Schlussfolgerung: Die Kombination von Sofosbuvir, Glecaprevir/Pibrentasvir und Ribavirin kann eine effektive Therapie nach Rückfällen auf eine vorherige DAA-Therapie darstellen, insbesondere, wenn ein SVR nach Gabe von Sofosbuvir, Velpatasvir und Voxilaprevir ausbleibt.

Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: A Case Report

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Key words: chronic hepatitis C virus infection, direct-acting antiviral therapy, resistance-associated species, voxilaprevir relapse, case report

Details and Comments: We confirm that the present manuscript is so far unpublished and is not under consideration by any other journal. It was elaborated in accordance with the principles outlined in the Declaration of Helsinki.

Abstract

Background: Relapses after therapy with direct-acting antiviral agents (DAA) in chronic hepatitis C virus (HCV) infections are rare due to high efficacy of interferon-free therapy regimens. The presence of resistance-associated substitutions (RAS) in proteins targeted by therapy can lead to lower rates of sustained virological response (SVR) in patients receiving DAA-therapy and few evidence exists as to how to treat these patients.

Case Summary: We present a case of a multi-drug-resistant HCV-genotype-3a-infection in a 50-year-old female without confirmed cirrhosis, but with advanced fibrosis (liver stiffness 11.6 kPa) and low viral load. Resistance testing revealed a Y93H mutation in the NS5A gene. Therapies using sofosbuvir and daclatasvir (1st), sofosbuvir, velpatasvir and ribavirin (2nd), and subsequently with sofosbuvir, velpatasvir, and voxilaprevir (3st) did not achieve SVR. Compliance was good with rapid negativity of HCV RNA at 4 weeks of treatment on all three occasions. No virological breakthrough was recorded with all regimens. As a rescue attempt, the patient received 24 weeks of sofosbuvir, glecaprevir/pibrentasvir, and weight-based ribavirin at 1000mg. With this approach she achieved SVR, but developed hepatocellular carcinoma.

Conclusion: The combination of sofosbuvir, glecaprevir/pibrentasvir and ribavirin could be a rescue therapy after previous relapses on DAA-therapy, especially in patients with relapse after therapy with sofosbuvir, velpatasvir and voxilaprevir.

1 Introduction

2 Chronic infection with the hepatitis C virus (HCV) is a worldwide major healthcare burden,
 3 which can lead to liver cirrhosis, hepatocellular carcinoma (HCC) and extrahepatic
 4 manifestations,^[1] particularly in patients infected with HCV-genotype 3.^[2] In the last decade
 5 therapy options for these patients have significantly improved due to the introduction of
 6 interferon-free medication with fewer adverse effects and rates of sustained virological
 7 response (SVR) close to 100%.^[3] Although only a proportion of HCV-infected individuals have
 8 been treated with directly-acting antiviral agents (DAA) worldwide, the benefits are already
 9 obvious with lower mortality rates and a declining fraction of HCV-infected patients on liver
 10 transplant waiting lists.^[4]

11 Relapses to standard first line therapies consisting of sofosbuvir (SOF) and velpatasvir (VEL)
 12 or glecaprevir/pibrentasvir (GLE/PIB) are rare, and most of these can be treated successfully
 13 with a combination of SOF/VEL and voxilaprevir (VOX).^[5] Relapse can occur due to
 14 insufficient compliance, drug-drug interactions alleviating antiviral efficacy, and the evolution
 15 of viral resistance selected by therapy. Difficulties can also arise from patients with cirrhosis
 16 and/or HCV-genotype 3 infection who require longer therapy and/or the addition of ribavirin
 17 for optimal outcomes.^[6] However so far, no approved treatment is available for the very few
 18 non-responders to VOX-containing treatments.

19 Here, we present the case of a female patient who experienced relapses to three DAA therapies
 20 and who was eventually treated successfully with a combination of SOF, VEL, GLE/PIB and
 21 ribavirin.

23 Case presentation

24 Patient characteristics

25 A 50-year-old female with chronic HCV Genotype 3a infection, most likely transmitted by
 26 intravenous drug abuse in the 1980s was referred to our liver out-patient clinic in 2015. She

denied blood-transfusions or regular alcohol consumption. No relevant comorbid condition was present, and her only regular medication was esomeprazol 20mg daily to treat gastroesophageal reflux. She had several spider angiomas on her chest and shoulders but revealed no extrahepatic manifestations of HCV infection or signs of thrombocytopenia.

Transient elastography showed advanced fibrosis (11.6 kPa, IQR 0.6 kPa, variability 5%, success rate 100%, equivalent to METAVIR F3), confirmed by a second measurement six weeks later (11.9 kPa). Prior to therapy transaminases were elevated (2-3x of the upper limit of norm), international normalized ratio (INR) was 1.26 and the HCV-RNA viral load was 160.000 IU/ml. Serology for human immunodeficiency virus (HIV) and replicating hepatitis B virus (HBV) infection were negative, but revealed an anti-HBc-alone constellation. Until this time, the patient had been HCV- treatment-naïve.

Therapy attempts not leading to SVR

In September 2015 our patient gave consent to start antiviral therapy. As recommended in former guidelines for HCV-genotype 3a,^[7] we started therapy with a daily combination of NS5A- (daclatasvir [DAC] at 60mg daily) and NS5B-inhibitors (SOF at 400mg daily) for 12 weeks. According to published evidence, this combination was reported to achieve SVR-rates of >95% in individuals without cirrhosis.^[8]

During therapy the patient was seen and monitored at weeks 4, 8 and 12, as well as 12 weeks after treatment termination by clinical and laboratory examination. Screening for HCC was performed by liver-sonography every six months. At first consultations she reported fatigue and symptoms of minor depression, which were successfully treated with a combination of 0.5mg flupentixol and 10mg melancantren (Deanxit®) daily. No evidence for impaired treatment adherence was found, especially since the patient showed a good initial response to therapy with HCV-RNA below detectable levels (<15U/ml) already 4 weeks after treatment start.

However, when SVR was assessed 12 weeks after treatment cessation the patient was found to have transaminitis and high viremia.

Therapy attempt	Duration	Medication	SVR
1	12 weeks	SOF + DAC	no
2	24 weeks	SOF + VEL + RIB	no
3	12 weeks	SOF + VEL + VOX	no
4	24 weeks	SOF + RIB + GLE/ PIB	yes

Abbreviations: *SOF* sofosbuvir, *DAC* daclatasvir, *VEL* velpatasvir, *RIB* ribavirin, *VOX* voxilaprevir, *GLE* glecaprevir, *PIB* pibrentasvir, *SVR* sustained virological response

Table 1: Characteristics of the therapy regimens used in the present case

Viral resistance was tested and a resistance-associated tyrosin (Y) to histidine (H) substitution (RAS) at position 93 of the amino acid sequence within the NS5A region (Y93H) was identified. The Y93H mutation in the NS5A region is relatively common in viral genotype 3a, affecting about 8% of patients with chronic HCV genotype 3a infection worldwide.^[9] It confers resistance towards DAC used in the present case and other NS5A-inhibitors, including elbasvir, velpatasvir, pibrentasvir and ledipasvir and may therefore explain the relapses to the various treatments in our patient.^[10] Through selection of resistant virus species by previous therapy the prevalence of RAS is much higher in patients with persisting HCV-infection after DAA-failure and can be found in about ¾ of these cases,^[11,12] depending on used medication, type of treatment failure and HCV genotype/subtype.^[13,14] The testing on RAS can facilitate choosing the right medication for retreatment^[15] and therefore is endorsed after failure of DAA-therapy.^[4] As recommended in former^[16] and current guidelines^[4] our 2nd line therapy also contained 400mg SOF daily. Although resistance to SOF has been described in patients with relapses after therapy, resistant virus clones do usually not persist for long beyond the end of therapy and

1 therefore have no clinical relevance for retreatment.^[17] Furthermore we changed NS5A-
2 inhibitor from DAC to velpatasvir (VEL) (100mg daily) and due to the advanced fibrosis, the
3 SOF-containing pre-therapy and the Y93H mutation, we added ribavirin (weight-based 1000mg
4 daily in two doses) and extended therapy duration to 24 weeks. For this combination excellent
5 rates of SVR were reported in previous studies, also in genotype 3, which were independent
6 from the presence of RAS.^[18,19]

7 Even though the viral load again fell below the level of detection during therapy without
8 evidence of virological breakthrough, a relapse with high viremia was recorded 12 weeks after
9 the end of treatment.

10 Considering the clear need for successful therapy in this patient, we opted for a 3rd line therapy
11 based on data of the POLARIS trials^[5] which showed SVR-rates of 96% (POLARIS-1) and
12 98% (POLARIS-4) for the triple combination of SOF + VEL and voxilaprevir (VOX) even in
13 retreatment scenarios after relapses on DAA-therapy. The reported excellent SVR rates in these
14 trials were independent from HCV-genotypes and presence of RAS and resulted in a
15 generalized recommendation of SOF + VEL + VOX for HCV-treatment after relapse from
16 DAA-therapy in current EASL-guidelines.^[4] Before therapy start, we changed PPI-therapy
17 from esomeprazol to omeprazol to avoid the well-known potential interactions with VOX
18 (www.hep-druginteractions.org). In April 2018 our patient commenced HCV treatment with
19 combination of SOF (400mg), VEL (100mg) und VOX (100mg), all taken once daily for 12
20 weeks. As presented in Figure 1, viral load again significantly decreased during therapy with
21 another relapse 12 weeks after end of therapy.

22 23 Successful therapy and outcome

24 Since no approved therapy is available for relapsers to VOX-containing therapies, an off-label
25 combination had to be considered. We decided to use the NS3/4A protease inhibitor glecaprevir
26 (GLE) coformulated with the NS5A inhibitor pibrentasvir (PIB) for an additional therapy

attempt for several reasons: First, previous studies achieved high SVR-rates with this once-daily, fixed-dose combination regimen^[20] also among patients with Y93H mutation and genotype 3.^[21] Secondly, PIB has demonstrated high *in vitro* antiviral activity in Y93H mutated viral strains^[22] and furthermore is independent from the stage of fibrosis in subjects without cirrhosis.^[20] Clinical trials yielded conflicting data whether an extension to longer therapy of GLE/PIB leads to higher SVR-rates,^[21,23] but at least showed that longer therapy duration is non-inferior to 8 or 12 week duration. Consequently, we extended therapy to 24 weeks again. Although several studies showed high SVR-rates in retreatment scenarios for the GLE/PIB alone,^[21,24] we added SOF and weight-based ribavirin, as proposed in current EASL-guidelines with regard to the results of the MAGELLAN-Trial.^[4,25] Again, our patient showed good initial response with decrease of transaminases and a viral load <15IU/ml. No side-effects were monitored and finally, SVR was achieved. Transaminases also stayed at normal levels, indicating termination of hepatitis. Unfortunately, sonographic HCC screening revealed a hypoechogenic lesion in liver segment II with a diameter of 26mm, which was confirmed by magnetic resonance tomography. The patient underwent successful partial liver resection, which confirmed HCC histologically.

Abbreviations: SOF sofosbuvir, DAC daclatasvir, VEL velpatasvir, RIB ribavirin, VOX voxilaprevir,

GLE glecaprevir, PIB pibrentasvir, SVR sustained virological response, ASAT – aspartate aminotransferase,

ALAT - alanine aminotransferase.

Figure 1: Development of transaminases and HCV-RNA-viral-load along therapy

Discussion

In the present case we report on a patient with a multi-drug resistant HCV-infection, most likely associated to RAS, in which several highly effective therapies had failed until finally the off-label combination consisting of SOF, GLE/PIB and ribavirin achieved SVR. To the best of our knowledge, this is the first published case with relapses after three different DAA regimens including VOX in a patient without confirmed cirrhosis.

Most likely, the observed multiple relapses after DAA-therapy were related to the Y93H mutation in the NS5A-gene recorded in our patient since no evidence for reduced compliance was found. Nevertheless, recent data temper the possible role of RAS on treatment failure,

especially for the combination of SOF + VEL (+ VOX) since with this therapy SVR-rates close to 100% were observed also in HCV-strains with RAS.^[19,26,27] Selection of viral resistance to DAAs is rarely observed and in combination with the high barrier to resistance in patients with RAS prior to therapy virological relapse seems uncommon. Further studies that investigate associations to therapy failure beyond the presence of RAS are required to improve treatment in cases such as the present one. In retrospective analysis the use of high-dose PPI was shown to be associated with lower rates of SVR, most likely due to impaired drug absorption at elevated gastric pH levels.^[28] Nevertheless, the effect of lower doses of PPI, as taken by our patient, is controversially discussed.^[29] Consequently, a small but pivotal effect on DAA-failure in our patient cannot be excluded.

Retrospectively, the 2nd therapy cycle could have been avoided by using the VOX-containing medication outright, as it was applied in the 3rd line therapy. However, the combination of SOF/VEL/VOX was not yet approved at that time. Currently, guidelines do not recommend the use of SOF + VEL in HCV genotype 3 neither in retreatment scenarios nor in patients with compensated cirrhosis.^[4] Our patient did not show cirrhosis, but clearly advanced fibrosis in transient elastography. Confirmation or exclusion of cirrhosis would have been possible only by biopsy, which the patient refused to have. We suspect that the presence of unrecognized cirrhosis also prevented SVR to the SOF + VEL therapy, and likewise caused failure of the first therapy containing SOF + DAC, as far as low response rates were observed in patients suffering from cirrhosis with this regimen, especially in those with genotype 3.^[8,30] Consequently current guidelines recommend the direct use of weight-based ribavirin added to the combination of SOF/VEL/VOX in retreatment scenarios in patients with cirrhosis.^[4]

Although only a few patients are affected, multiple antiviral therapies are associated with immense health costs. Moreover, the costs of second-, third- or even fourth-line therapy require a specific declaration of cost takeover by the responsible health insurance company in Switzerland. The aim of the present case report is therefore to provide evidence for

effectiveness of further DAA-therapy after the failure of several unsuccessful therapy attempts, especially in cases with relapse after the combination of SOF + VEL + VOX. So far there is only rare experience in retreating these patients and it exists no evidence in choosing the best medication. In accordance to the preliminary data of two ongoing trials^[31,32] the used combination SOF + PIB + GLE + RIB could be the best option in patients with multiple-drug resistant HCV-infection. As the present case report shows, the delay or renouncement of further DAA-therapy might be able to save initial costs but leads to a higher risk of developing HCC, also present in patients without cirrhosis. Considering HCV-genotype, RAS and patient characteristics remains fundamental to choose the best medication and provide effective therapy in such cases.

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